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Serious iatrogenic complications: pulmonary vein stenosis after ablation of atrial fibrillation

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Pulmonary vein stenosis (PVS) has been recognized as a clinical entity complicating radiofrequency or cryoenergy ablation for atrial fibrillation. Although reduced by technical and procedural advancements, this complication portends remarkable morbidity and presents insidiously with non-specific symptoms causing frequent misdiagnosis and wrong management that lead to detection delay and major adverse implications. Non-invasive imaging is key for timely diagnosis and transcatheter procedural planning. Most recent consensus on severe and symptomatic PVS management indicates that stenting is the preferred treatment because of superior long-term patency compared to balloon angioplasty, particularly in patients with larger reference vessel diameter. However, the rate of recurrent stent restenosis is high and remains a great challenge. Goal of our manuscript is to provide a comprehensive review regarding pathophysiology, detection, treatment, and prevention of this serious iatrogenic complication.

Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia worldwide, is responsible for substantial morbidity and mortality. After Haïssaguerre *et al.*[1] landmark study in 1998, catheter ablation (CA) with radiofrequency (RF) and more recently cryoenergy has been established as a cornerstone treatment for symptomatic patient with paroxysmal or persistent AF unresponsive or intolerant to medical therapy. Currently, more than 50 000 CA are performed for AF each year in Europe. With the widespread introduction of this technique, pulmonary vein stenosis (PVS) complicating CA emerged as a new syndrome in the late 1990s.[2] Incidence of severe PVS has fallen from 30% to 40% reported in early studies to between 0.29% and 3.4% after 2000 due to improved catheter technology and ablation strategy evolution.[3] Nevertheless, the real occurrence is likely underestimated because this complication is underreported, moderate or even severe PVS may be asymptomatic, and imaging studies are often performed only in symptomatic patients. Indeed, the Heart Rhythm Society consensus statement no longer recommends routine screening after CA, but rather endorse a symptom-guided approach to imaging.[4] Although PVS is rare, it will continue to affect many patients since AF prevalence is expected to grow with population aging, while in the 'real world' CA will be performed even in low-volume and less experienced centres, potentially leading to progressive increase in complications such as PVS.

Pathophysiology

The PVS histopathology remains poorly defined. A likely cause is intense periadventitial inflammation with

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collagen deposition and neointimal hyperplasia leading to scarring and pulmonary vein (PV) shrinkage due to the thermal injury caused by RF energy delivered within the PV ostia or at the PV-antrum junction.[5] This has been documented by computed tomography (CT) showing extensive fibrosis of PV perihilar tissue and animal studies revealing a cascade of inflammatory protein precursors. The PV tissue appears to be particularly reactive to injury, with a greater fibrotic reaction than that typically seen in other cardiovascular tissues. Although some studies have shown a predilection for younger patients, further investigation is needed to determine whether PV vulnerability varies with age. The fibrotic build up process leading to stenosis can take 6–12 months to reach the steady state, which accounts for the progressive nature of PVS during this time. Further progression beyond this period may occur at a slower pace, but it is less documented. Although the fibrotic reaction may be sufficient to cause PV occlusion (PVO), two other factors, either singly or in combination, may contribute, namely stenosis length and thrombus formation. When PV non-pulsatile and low-pressure flow is reduced below a certain threshold, there may be a propensity for thrombosis as the blood flows sluggishly through a severe narrowing, particularly in a long stenosis. In addition to local narrowing, a vascular occlusive process characterized by intimal hyperplasia and medial thickening of large and small PVs and arteries has been observed histologically, suggesting progressive and irreversible atrophy/hypoplasia of upstream PV branches and their tributaries.[6] This, combined with thrombosis, may be the final pathway leading to complete obliteration of PVs and their branches. Furthermore, PVS-induced venous congestion can reduce perfusion to the affected lung segment that in severe cases may cause irreversible pulmonary damage.[6] In these conditions, the parenchyma is congested with alveolar haemorrhage and interstitial septal thickening. Several studies suggest that PVS risk may be dose dependent rising with each subsequent RF exposure. It is also notable that the left-sided PVs are affected more frequently than the right-sided PVs. Although the reason of the disproportionate involvement has not been clarified, it may be attributable to the smaller diameter of the left inferior PV, the cranial orientation of the left superior vein ostium, and the position of the left atrium (LA) ridge near the LA appendage, leading to ablation inside the left PVs or closer to the vein ostium.

Clinical presentation and delayed diagnosis

Clinical presentation of PVS is variable and depends upon several factors including number of involved PVs, PVS severity, length and time course, the response of the entire pulmonary vasculature, and the presence and extent of collaterals. Many patients with isolated or mild PVS are asymptomatic. This could be explained by the ability of the pulmonary circulation to develop compensatory mechanisms, including pulmonary haemodynamic changes and blood flow redistribution with neovascularization of the ipsilateral lung. Patients with more extensive and severe PVS may present with insidious non-specific pulmonary complaints over the months after CA resulting in misdiagnosis.[7] Incorrect diagnosis is common because most frequent symptoms, including dyspnoea on exertion or even at rest, pleuritic and exertional chest pain, dry cough, decreased exercise tolerance, flu-like malaise, and haemoptysis, are non-specific and mimic other more prevalent pulmonary diseases.[7] Some patients develop significant pleural effusion, often recurring despite drainage until PVS is relieved. Moreover, CT may show multifocal peripheral opacities or nodular lesions consistent with venous infarction or alveolar haemorrhage, interstitial septal thickening and parenchymal bands resulting from fibrous connective tissue hyperplasia, and intimal hypertrophy of venules. These alterations are specifically seen in the chronic phase of pulmonary venous obstruction. The parenchymal abnormalities may be easily misdiagnosed as pneumonia, tuberculosis, lung cancer, or pulmonary embolism. Thus, patients are often referred to pulmonologists instead of cardiologists. The former physicians may have a low index of clinical suspicion for this iatrogenic disease and may recommend multiple examination including bronchoscopy and thorascopic biopsy, along with inappropriate pharmacological treatments (e.g. antibiotics, antituberculosis drugs, or anticoagulants) or even lobectomy. In the largest published series, 33% of PVS patients were initially diagnosed with bronchitis, pneumonia, or malignancy leading to unnecessary invasive diagnostic testing and delayed care.[8] Of note, delayed diagnosis can result in critical luminal loss and progression to PVO, with irreversible pulmonary damage that frequently are life-altering conditions because of severe and refractory symptoms. Prompt recognition of the PVS syndrome and early referral to an interventional cardiologist could theoretically avert unnecessary procedures and ineffective treatments as well as preventing PVO. Notably, ~21% of patients with severe PVS experience recurrent symptomatic AF or atrial flutter.

Non-invasive evaluation

Non-invasive diagnostic modalities in patients with suspected PVS include computed tomography angiography (CTA), magnetic resonance angiography (MRA), transoesophageal echocardiography (TEE), and ventilation/perfusion (V/Q) scanning.[9]

Computed tomography angiography

Contrast-enhanced, electrocardiography-gated CTA is most commonly employed because of better sensitivity due to high spatial resolution. It provides fast multiplanar and three-dimensional reconstruction of PVs and LA allowing PVS diagnosis and procedural planning (*Figure 1A* and *B*). Further, PVS-associated lung parenchymal and vascular alterations may be assessed. The main advantages over MRA are quicker image acquisition, lower cost, and more accurate detection and quantification of PVs, including stent restenosis assessment. Optimized CTA protocols are essential, and the reading cardiologist or radiologist should have an

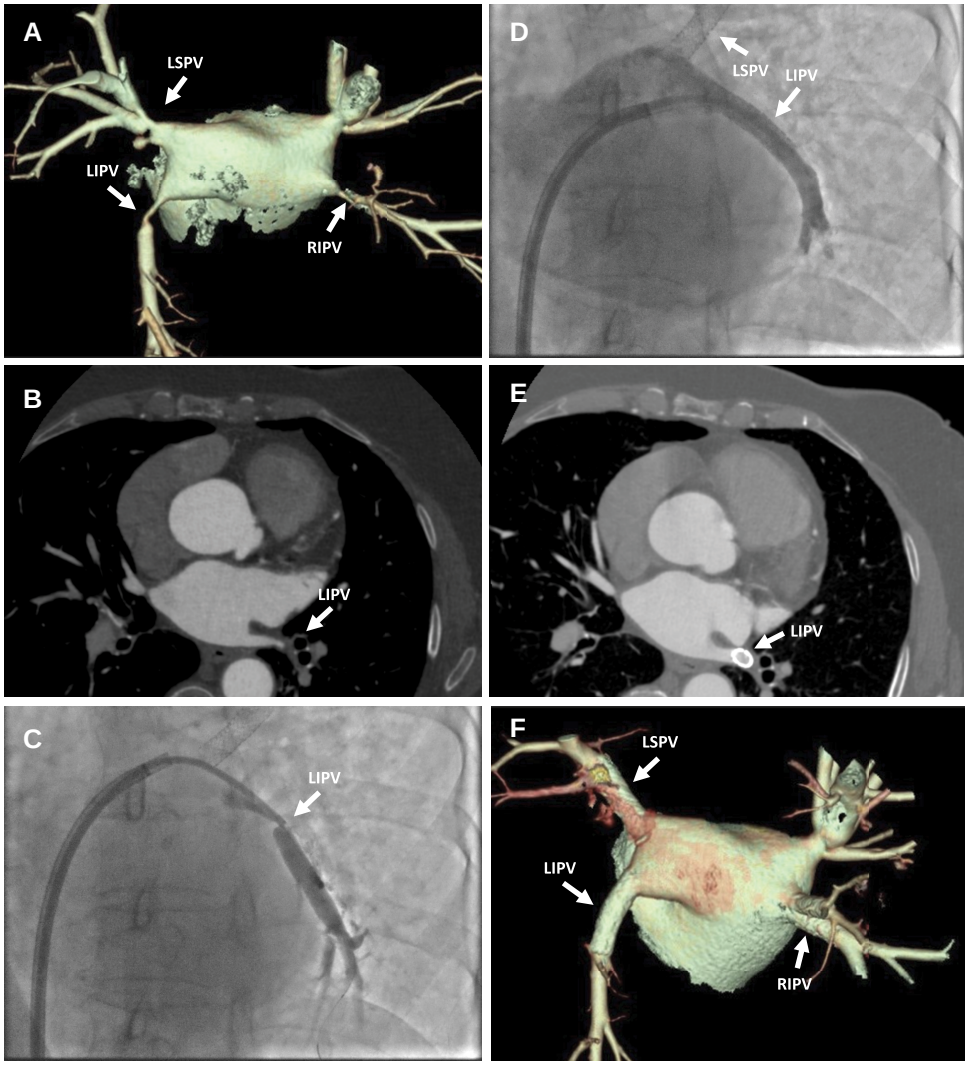
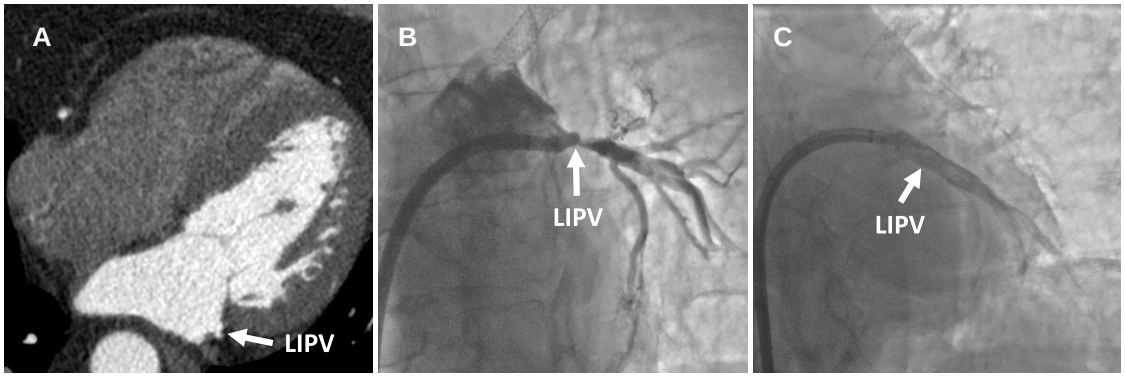


Figure 1 (*A*) Forty-four-year-old woman was referred to our hospital one year after radiofrequency catheter ablation for atrial fibrillation. She previously underwent bronchoscopy and thorascopic biopsy in another centre to investigate dyspnoea, haemoptysis, and multifocal opacities of lung parenchyma detected at chest X-ray. We performed CTA with three-dimensional reconstruction that revealed severe stenosis of the left inferior, left superior, and right inferior pulmonary veins (arrows) (*A*). Severe stenosis of the left inferior pulmonary vein shown by axial CTA (*B*) was confirmed at invasive angiography (arrows) (*C*). Interventional treatment with balloon angioplasty and implantation of peripheral bare-metal stents was performed with good angiographic (*D*) and CTA (*E* and *F*) results (arrows). Patient's symptoms disappeared after the procedure. LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein.

understanding of local anatomy and the training required for PVS diagnosis. This is particularly the case in asymptomatic patients when a low suspicion index may be present. Limitations include radiation exposure and contrast dose, especially in serial imaging. Moreover, CTA tends to overestimate PVS severity and PVO. The left inferior PV in particular may be diagnosed as having a stenosis following CTA, when in fact, no such stenosis is present, which may lead to inappropriate invasive evaluation. Sometimes what appears to be a PVO is shown on angiography to be a PVS with a tiny opening allowing passage of dedicated coronary wires that may be followed by balloon angioplasty (BA) and stent deployment when appropriate. Thus, when CTA shows a PVO with an otherwise favourable anatomy for intervention, invasive angiography should be considered (*Figure 2*).

Magnetic resonance angiography

Contrast-enhanced MRA offers multiple advantages such as radiation-free evaluation, which is of particular importance given the frequency with which younger patients may undergo surveillance imaging, three-dimensional visualization of PVs and adjacent mediastinal structures, and information about pulmonary arterial flow redistribution and left and right ventricular function. Like CTA, MRA yields volumetric three-dimensional images to facilitate intraprocedural guidance, and LA appendage thrombus is well assessed simultaneously. Limitations include lower spatial resolution, longer scanning time, and reduced access compared with CTA. Moreover, pacemaker and implantable cardioverter defibrillator, whose use is not rare in FA patients, do not allow MRA if they are of an older generation, while artefacts may compromise image quality with newer MRA-compatible devices.



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- **Preplanning of fluoroscopic angles with CTA is crucial to optimize ostial and distal vessel visualization.**
- **Favourable angioplasty factors include:**
  - **Presence of a proximal "beak-like" entry point to localize the PV ostium;**
  - **Short length of the occlusion;**
  - **Presence of clear distal vessel targets.**
- **Use of coronary CTO devices (e.g., dedicated wires, microcatheters) may be helpful.**

Figure 2 CTA showed total occlusion of the left inferior pulmonary vein (arrow) in a 38-year-old man eight months after catheter ablation for atrial fibrillation (*A*). Note the 'beak-like' entry point (arrow). Invasive angiography showed pulmonary vein subocclusion with a residual tiny opening (arrow) (*B*) that allowed passage of a coronary wire followed by balloon angioplasty and deployment of a peripheral bare-metal stent (arrow) (*C* and *D*): key points to assess the technical feasibility and procedural strategies for the interventional treatment of pulmonary vein total occlusion. CTA, computed tomography angiography; CTO, coronary total occlusion.

Transoesophageal echocardiography

This imaging modality provides visualization and assessment of stenosis severity and flow velocity, the latter of which is obviously of functional significance. A PVS presents as narrowed PV ostium, elevated diastolic peak velocity (>0.9–1.1 m/s) on pulsed-wave Doppler, and turbulent flow. One study comparing TEE with CTA showed 86% sensitivity and 95% specificity in PVS detection at peak velocities of 100 cm/s.[10] Although TEE is less accurate than CTA and MRA in defining PVS degree, advantages include lack of ionizing radiation and availability of both anatomic and functional data. However, PV visualization is limited to the ostia and can be technically challenging, requiring operator expertise. Moreover, no standard TEE criteria for PVS severity exist.

V/Q scanning

Radionuclide V/Q uses technetium-99m macroaggregated albumin to interrogate pulmonary blood flow, delineating the impact of PVS on pulmonary perfusion and serving as a useful physiologic adjunct to anatomic imaging. Severe (>70–80%) PVS is shown as a ventilation/perfusion mismatch due to blood flow redistribution to unaffected areas. Moreover, lobar perfusion can be quantified as percentage of total pulmonary blood flow, which may facilitate functional change monitoring after intervention. However, V/Q scanning may not detect less severe PVS, although it can help stratify those with indeterminate stenoses by imaging. Of note, other pathologies affecting pulmonary blood flow may thwart V/Q imaging utility.

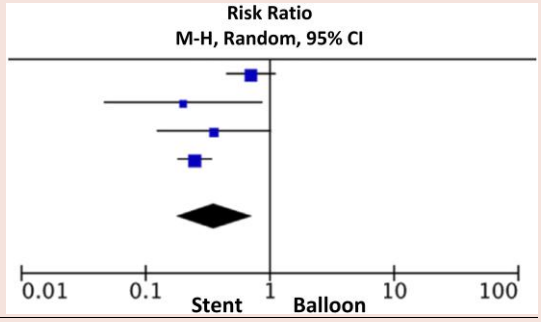
Treatment

No dedicated guidelines exist that can indicate optimal treatment strategy, reflecting the absence of randomized trials on PVS management. Similarly, there is no consensus about treatment of asymptomatic patients with a single PVS. However, imaging monitoring every 3–6 months is recommended in cases with a 50–85% stenosis. According to most authors, patients with symptomatic severe (>70%) stenosis of one or multiple PVs should be treated (*Figure 1C*). Transcatheter intervention with either BA or peripheral bare-metal stent (BMS) implantation is the preferred treatment and is associated with high acute success, low complication rates and significant subjective improvement (*Figure 1D–F*). However, both approaches are limited primarily by restenosis, which may be a serious recurring problem that remains to be solved. Acute elastic recoil is commonly observed immediately after BA and may contribute to earlier restenosis, while neointimal hyperplasia may account for the later restenosis reported after stenting. Available data suggest that stenting is associated with a significant reduction of restenosis rate[10-13] (*Table 1*). Restenosis risk factors include small reference vessel diameter and longer time from CA to intervention. Evidence of this are several studies showing long-term patency rates of ~80% in PVS treated with stents that were at least 10 mm in diameter.[14] These findings indicate that early PVS diagnosis and prompt referral for stenting when the vessel diameter allows use of larger stents are critical for improved outcomes. Indeed, time from CA to

intervention is inversely associated with PV diameter[14] and late diagnosis increases the risk of diffuse hypoplasia of upstream PVs leading to PVO. Although catheter intervention is often possible in PVO (*Figure 2*), some cases are not treatable. For smaller PVs, BA can be performed in the hope that flow improvement may promote vessel growth allowing stent implantation a few months later. It is important to utilize stents with good radial strength that can be redilated to larger diameters. This permits further stent expansion at a subsequent procedure if there has been growth of the upstream vessel, thereby decreasing the restenosis risk. Covered stents have been used in some patients and can certainly be utilized to treat a tear emergently, but long-term follow-up of these devices is still very limited. There are few data on coronary drug-eluting stent (DES) use, which could be appealing to limit neointimal proliferation. However, considering that the diameter of DES does not exceed 5 mm, they are too small in most cases and available data indicate inferior outcome compared to larger diameter BMS. The first-line treatment of stent restenosis is BA. Cutting balloon angioplasty and drug-coated balloons have not been extensively studied, but may offer a promising approach for recurrent stent restenosis. Although no guidance on postintervention antithrombotic therapy is available,

Table 1 Observational studies comparing restenosis rates after PVS stenting vs. balloon angioplasty.

First author, year	Balloon angioplasty (*n*)	Stent (*n*)	Median follow-up	Risk ratio (RR) for restenosis (95% CI)
Fender *et al.*, 2020[10]	88	81	55.2	0.70 [0.45-1.10]
Hill *et al.*, 2013[11]	7	7	13	0.20 [0.05-0.86]
Schoene *et al.*, 2018[12]	68	16	60	0.35 [0.12-1.01]
Suntharos *et al.*, 2020[13]	62	250	17	0.25 [0.18-0.34]
Total	225	354	N/A	0.36 [0.15-0.86]



PVS, pulmonary vein stenosis; M-H, Mantel-Haenszel; N/A, not available.

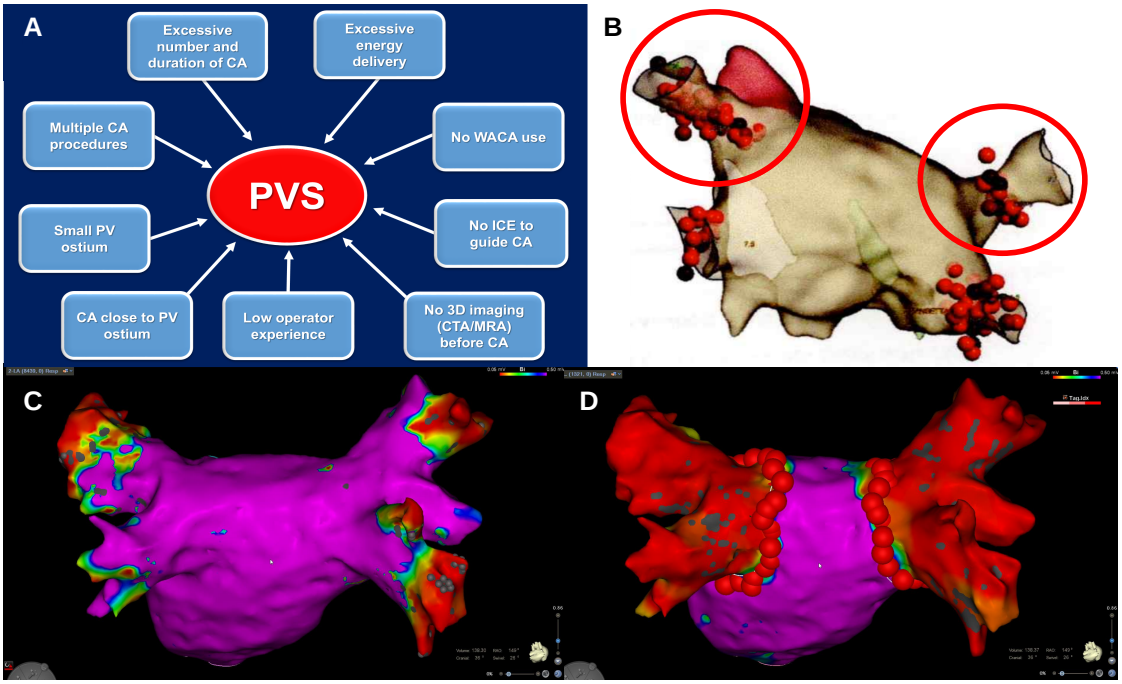


Figure 3 Risk factors that can promote pulmonary vein stenosis after catheter ablation of atrial fibrillation (*A*). Ablation with radiofrequency energy delivered within the PV ostium (circles) (*B*). Carto system-guided high-density electro-anatomic mapping (*C*) and circumferential ablation at the antral level of the pulmonary veins (red dots) (*D*). CA, catheter ablation; ICA, intracardiac echocardiography; CTA, computed tomography angiography; 3D, three-dimensional; MRA, magnetic resonance angiography; PV, pulmonary vein; PVS, pulmonary vein stenosis; WACA, wide area catheter ablation.

dual-antiplatelet therapy for 3–6 months is generally prescribed followed by aspirin monotherapy, while when oral anticoagulation (OAC) is indicated, clopidogrel or aspirin monotherapy plus OAC is used. As with any interventional procedure, PVS treatment may have potential, albeit rare, complications. They include wire perforation or PV rupture with tamponade, stent embolization into the LA due to wrong stent sizing or positioning, cerebrovascular accident and acute myocardial ischaemia due to thromboembolism, stent thrombosis, pleural effusion, and self-limiting haemoptysis and pulmonary haemorrhage. In case of relentless restenosis, surgical treatment with patch venoplasty is an option. However, when complete loss of perfusion of the affected pulmonary lobe occurs, especially in association with thrombosis, lobectomy may be required.

Prevention

Because of the challenges in diagnosis and treatment, PVS prevention should be the highest goal. A thorough evaluation, including CTA or MRA to assess PV anatomy and size, could be useful at least in less experienced centres before CA to identify PVS risk factors (*Figure 3A*). Over the past two decades, shifting CA from PVs (*Figure 3B*) to the ostial and subsequently to the antral level guided by a multipolar mapping catheter (*Figure 3C*) resulted in a significant reduction in PVS incidence. Moreover, limiting ablation number and duration, choosing energy source and power settings, using intracardiac echocardiography to guide power titration, monitor CA position, and selecting the optimal device in relation to PV morphology and size may minimize the trauma reducing PVS risk. In case of cryoballoon (CB) use for large PVs, the CB tends to travel more deeply, so either other devices should be selected or segmental non-occlusive CB ablation should be performed to avoid freezing inside the PVs. Unlike CB, hot balloon (HB) and laser balloon have variable sizes that can be adjusted for more proximal ablation. Measuring HB surface temperature allows selection of appropriate energy settings based on PV size and wall thickness that may reduce excessive ablation. Finally, initial data suggest that pulsed field ablation (PFA) may be a promising technique to reduce PVS risk. This novel, non-thermal ablative modality applies pulsed electric fields that produce pores in the phospholipid cell membrane that lead to irreversible breakdown of membrane structure and ultimately cell death. Of note, the first randomized trial comparing PFA vs. thermal ablation (RF or cryoenergy) demonstrated statistically less PV narrowing.[15]

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Data availability

No new data were generated or analysed in support of this research.

Disclaimer

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References

1. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G *et al*. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–666.
2. Saad EB, Marrouche NF, Saad CP, Ha E, Bash D, White RD *et al*. Pulmonary vein stenosis after catheter ablation of atrial fibrillation: emergence of a new clinical syndrome. *Ann Intern Med* 2003;**138**:634–638.
3. Cappato R. Pulmonary vein stenosis following radiofrequency ablation of atrial fibrillation: has it become a clinically negligible complication? *JACC Clin Electrophysiol* 2017;**3**:599–601.
4. Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L *et al*. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017;**14**:e275–e444.
5. Taylor GW, Kay GN, Zheng X, Bishop S, Ideker RE. Pathological effects of extensive radiofrequency energy applications in the pulmonary veins in dogs. *Circulation* 2000;**101**:1736–1742.
6. Yang H-M, Lai CK, Patel J, Moore J, Chen P-S, Shivkumar K *et al*. Irreversible intrapulmonary vascular changes after pulmonary vein stenosis complicating catheter ablation for atrial fibrillation. *Cardiovasc Pathol* 2007;**16**:51–55.
7. Packer DL, Keelan P, Munger TM, Breen JF, Asirvatham S, Peterson LA *et al*. Clinical presentation, investigation, and management of pulmonary vein stenosis complicating ablation for atrial fibrillation. *Circulation* 2005;**111**:546–554.
8. Fender EA, Widmer RJ, Hodge DO, Cooper GM, Monahan KH, Peterson LA *et al*. Severe pulmonary vein stenosis resulting from ablation for atrial fibrillation: presentation, management, and clinical outcomes. *Circulation* 2016;**134**:1812–1821.
9. Simard T, Sarma D, Miranda WR, Jain CC, Anderson JH, Collins JD *et al*. Pathogenesis, evaluation, and management of pulmonary vein stenosis: JACC review topic of the week. *J Am Coll Cardiol* 2023;**81**:2361–2373.
10. Fender EA, Widmer RJ, Mahowald MK, Hodge DO, Packer DL, Holmes DR Jr. Recurrent pulmonary vein stenosis after successful intervention: prognosis and management of restenosis. *Catheter Cardiovasc Interv* 2020;**95**:954–958.
11. Hill J, Qureshi AM, Worley S, Prieto LR. Percutaneous recanalization of totally occluded pulmonary veins after pulmonary vein isolation-intermediate-term follow-up. *Catheter Cardiovasc Interv* 2013;**82**:585–591.
12. Schoene K, Arya A, Jahnke C, Paetsch I, Nedios S, Hilbert S *et al*. Acquired pulmonary vein stenosis after radiofrequency ablation for atrial fibrillation: single-center experience in catheter interventional treatment. *JACC Cardiovasc Interv* 2018;**11**:1626–1632.
13. Suntharos P, Worley SE, Liu W, Siperstein M, Prieto LR. Long-term outcome of percutaneous intervention for pulmonary vein stenosis after pulmonary vein isolation procedure. *Catheter Cardiovasc Interv* 2020;**95**:389–397.
14. Raeisi-Giglou P, Wazni OM, Saliba WI, Barakat A, Tarakji KG, Rickard J *et al*. Outcomes and management of patients with severe pulmonary vein stenosis from prior atrial fibrillation ablation. *Circ Arrhythm Electrophysiol* 2018;**11**:e006001.
15. Mansour M, Gerstenfeld EP, Patel C, Natale A, Whang W, Cuoco FA *et al*. Pulmonary vein narrowing after pulsed field versus thermal ablation. *Europace* 2024;**26**:euae038.